



# Narrative review of the emerging role of molecular biomarkers in guiding the definitive management of unresectable non-small cell lung cancer

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**Abstract:** The addition of PD-L1 targeting consolidation therapy to previously standard of care concurrent chemoradiation for locally advanced, unresectable non-small cell lung cancer resulted in dramatic improvements in clinical outcomes. However, in contrast to patients with metastatic disease, the application of immunotherapies is not currently guided by molecular characteristics of patient tumors. Furthermore, despite increasing awareness of predictive and/or prognostic genomic alterations in patients with locally advanced disease, the utility of targeted therapies, such as those aimed at alterations in *EGFR* or *ALK*, remains unclear in this subset of patients. As a result, patients with unresectable, locally advanced non-small cell lung cancer are treated uniformly according to histology, regardless of other molecular features despite the potential for treatment-associated risks without a clear benefit. Here, we first discuss the advantages of utilizing molecular biomarkers to guide treatment of non-small cell lung cancer based on treatment outcomes in the metastatic setting. Next, we review preclinical and retrospective clinical data that supports potential further personalization of these treatment strategies in earlier stages of disease. Finally, we discuss some of the ongoing clinical trials attempting to address these hypotheses prospectively.

**Keywords:** Immunotherapy; targeted therapy; unresectable non-small cell lung cancer (unresectable NSCLC)

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## Introduction

Eighty-five percent of all lung cancer diagnoses are non-small cell lung cancer (NSCLC), with approximately one-third of these cases presenting as locally advanced disease (1). The results of the PACIFIC trial (NCT02125461) redefined the standard of care for unresectable, locally advanced NSCLC by demonstrating that consolidation with durvalumab following concurrent chemotherapy and radiation therapy (CCRT) resulted in improved progression-free survival (PFS) and overall survival (OS) (1,2). In fact, the PACIFIC trial demonstrated a 12-month PFS of 56% with durvalumab as compared to 35% with placebo. Although a significant improvement, 44% of patients still progressed or died within the first

year of treatment. This represents an unmet need for novel treatment strategies in these potentially curable patients.

Over the years, the identification of molecular biomarkers has offered both predictive and prognostic insight into the outcomes of patients with metastatic NSCLC. Subsequent utilization of these biomarkers has helped tailor therapy for patients and maximize the therapeutic benefit derived from a particular treatment regimen. As a result, it is now essential to perform biomarker testing in the metastatic setting to identify actionable genetic variants. Targeted agents have only increased with time and have proven to effectively decrease tumor burden and improve the quality of life for many patients. At present, FDA approved targeted therapies in the metastatic setting are available for

**Table 1** FDA approved targeted therapies for metastatic NSCLC as of 10/2020

Target	FDA approved drugs
<i>ALK</i> rearrangement	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
<i>BRAF</i> V600E	Dabrafenib, dabrafenib/trametinib, vemurafenib
<i>EGFR</i> sensitizing mutation	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib
<i>MET</i> exon 14 skipping mutation	Capmatinib, crizotinib
<i>NTRK</i> gene fusion	Entrectinib, larotrectinib
<i>RET</i> rearrangement	Cabozantinib, pralsetinib, selpercatinib, vandetanib
<i>ROS1</i> rearrangement	Ceritinib, crizotinib, entrectinib, lorlatinib

NSCLC, non-small cell lung cancer.

molecular alterations in the following genes: *EGFR*, *ALK*, *ROS1*, *NTRK1*, *BRAF*, *RET*, and *MET* (Table 1). Promising data evaluating the safety and efficacy of a *KRAS* G12C inhibitor was also recently published in the literature (3). It is also important to note that upfront PD-L1 expression testing should be performed in all patients with metastatic NSCLC before first-line therapy is administered.

Although our care for patients with metastatic NSCLC now routinely incorporates a personalized approach to treatment based on molecular profiling of the tumor, a similar treatment approach has not been the standard practice for our patients with locally advanced disease. In the future, molecular profiling may no longer be restricted to just the metastatic setting, as its role in earlier stage disease is becoming more relevant. As an example, the recently published results of the *ADAURA* trial demonstrated a potential role for adjuvant osimertinib in patients with stage IB to IIIA *EGFR*-mutant NSCLC following previous surgical resection (4). Results from the trial demonstrated a very significant disease-free survival benefit for adjuvant osimertinib and may prove to change practice in the treatment of this patient population. Longer follow-up and data about sites of disease recurrence, however, are still needed to determine if this benefit will ultimately translate into improvements in OS and quality of life.

Currently, the standard of care management of unresectable locally advanced NSCLC involves the administration of definitive CCRT followed by durvalumab as consolidation immunotherapy (1). Notably, durvalumab is not recommended for patients who have had definitive surgical resection. NCCN guidelines recommend that if patients do plan to receive durvalumab but have not received full-dose chemotherapy concurrently with radiation therapy, then consolidation chemotherapy should be avoided given the increased risk of pneumonitis if patients are also to receive durvalumab. Alternatively, if patients will not be receiving

durvalumab because they are ineligible for immunotherapy, consolidation chemotherapy may be considered after CCRT has been completed. The following review article will explore the use of various biomarkers to personalize this standard approach for the treatment of patients with stage III unresectable NSCLC. We present the following article in accordance with the Narrative review checklist (available at <http://dx.doi.org/10.21037/tlcr-20-330>).

### PACIFIC trial

The PACIFIC trial was a pivotal study that evaluated the use of immune checkpoint blockade in patients with locally advanced NSCLC (1). In the study, 713 patients who had been treated with at least two cycles of platinum-based chemotherapy with radiation and were without evidence of disease progression were randomized in a 2:1 ratio to receive durvalumab at 10 mg/kg every 2 weeks for up to 1 year or to receive placebo. The primary endpoints of the study were defined as PFS and OS. At a median follow-up of 14.5 months, the PFS in the intent-to-treat population was significantly improved at 16.8 months in the durvalumab consolidation arm as compared to 5.6 months in the placebo arm (HR =0.52, P<0.001). In 2018, updated results from the PACIFIC trial demonstrated that after a median follow-up of 25.2 months, OS in the intent-to-treat population was significantly improved in patients treated with durvalumab as compared to treatment with placebo (HR =0.68, P=0.0025) (2).

Results of the PACIFIC trial were indeed practice-changing, as it significantly transformed the standard of care for locally advanced, unresectable NSCLC. Prior to the PACIFIC trial, the standard of care in this setting had been a combination of at least two cycles of platinum-based chemotherapy along with concurrent radiation therapy to visible disease and the mediastinum for a total of 6–7 weeks

of therapy with a cure rate of 20–25%. Now, as a direct result of the PACIFIC trial, all immunotherapy-eligible patients with locally advanced NSCLC who have completed definitive CCRT should receive durvalumab for 1 year given its overall tolerability and striking PFS and OS benefit.

In an attempt to better understand which patients benefit most from durvalumab consolidation after CCRT, a prespecified analysis of outcomes with respect to PD-L1 expression was conducted with a 25% cutoff point. PD-L1 testing was performed using the Ventana SP263 immunohistochemical assay on patients' archival tumor tissue obtained prior to CCRT. The subgroup analysis of OS benefit showed that with a PD-L1 expression of 25% as a defined cutoff point, treatment with durvalumab was associated with an improvement in PFS regardless of the tumor's PD-L1 expression, with a HR =0.59 for PDL1 expression level <25% and HR 0.41 for a PD-L1 expression level of ≥25%.

As part of an unplanned post hoc analysis, patients with PD-L1 expression of less than 1% demonstrated a trend towards failing to achieve an OS benefit from durvalumab consolidation. Specifically, patients with PD-L1 ≥1% had a HR =0.53 (95% CI: 0.36–0.77) favoring the durvalumab arm, as compared to patients with PD-L1 <1% had a HR =1.36 (95% CI: 0.79–2.34) favoring treatment with placebo. Although these results are hypothesis generating, it is important to keep in mind that the PACIFIC trial was not designed to evaluate the efficacy of durvalumab consolidation with regards to PD-L1 expression and it did not prospectively stratify patients at time of randomization by PD-L1 status. Additionally, the trial studied a limited number of patients with tumor PD-L1 expression of <1% (n=148). Furthermore, not all patients in the PACIFIC trial provided tumor tissue for assessment of PD-L1 expression; whereas for those that did, PD-L1 testing was performed on tissue obtained prior to CCRT, which may not be entirely representative of the tumor microenvironment changes and changes in PD-L1 expression that occur secondary to CCRT (5,6). Nevertheless, these results raise concerns about the use of the PACIFIC regimen irrespective of PD-L1 expression and could have potential implications for patient selection in the future.

Concerning patient enrollment, it is important to note that the PACIFIC trial did not exclude patients on the basis of next generation sequencing, including those with EGFR mutations or ALK translocations. Although the number of patients harboring these driver mutations was limited, subgroup analysis of patients based on their EGFR mutation status showed that while EGFR-mutated patients still

avored treatment with durvalumab, the trend was towards a more modest benefit. Specifically, the PACIFIC trial included 43/713 patients (6%) with EGFR-mutated disease. Subgroup analysis of PFS with regards to EGFR mutation status revealed that patients with a known EGFR mutation had a HR =0.76 (95% CI: 0.35–1.64) as compared to patients with a wild-type EGFR status who had a HR =0.47 (95% CI: 0.36–0.60). Clinically, like the aforementioned results with PD-L1, these results are difficult to interpret, but are provocative considering the role that driver mutations might play in the treatment of locally advanced NSCLC.

For now, the PACIFIC regimen remains the standard of care for treatment of our unresectable locally advanced NSCLC patients, regardless of genomic or proteomic biomarkers. We are still awaiting further studies to better determine more personalized treatment options for patients in this setting based on molecular profiling. Additionally, the decision to continue with durvalumab consolidation beyond 1 year remains challenging and is ultimately a discussion to be had between patients and their providers.

### **KRAS-mutant NSCLC**

Beyond the PACIFIC trial, additional studies have investigated how best to utilize known biomarkers when identifying treatment options for patients with unresectable locally advanced NSCLC. One such biomarker is KRAS mutation status. Clinically, KRAS is the most commonly mutated oncogene in NSCLC. There are multiple KRAS-mutant subtypes of NSCLC that are largely defined by co-mutations in TP53 and LKB1 (STK11) (7). LKB1/STK11 is a tumor suppressor gene involved in the AMPK-mTOR pathway that directly impacts cell growth and metabolism. Previous studies have shown that KRAS-mutated tumors harboring co-mutations in STK11 are often resistant to conventional treatment modalities consisting of chemotherapy and radiation (8–11). Skoulidis *et al.* additionally demonstrated that LKB1 (STK11) promotes resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma murine models (12). Specifically, the investigators showed that alterations in LKB1 were associated with a lack of PD-L1 expression in tumor cells across multiple cohorts, despite an intermediate or even high tumor mutational burden (TMB); additionally, there were lower concentrations of infiltrating CD8<sup>+</sup> cytotoxic T lymphocytes in both human and murine LKB1 deficient tumors. The mechanism of poor PD-L1 expression and T cell infiltration is thought to be secondary to epigenetic silencing of the stimulator of interferon genes (STING)

pathway, which is known to have an essential role in innate immunity. Loss of *LKB1/STK11* results in suppression of the STING pathway, resulting in decreased PD-L1 expression and T-cell recruitment (13). To improve upon treatment response rates, Wang *et al.* explored how best to sensitize *KRAS-STK11* mutant tumors to radiation, and showed that this specific subtype of NSCLC is sensitive to a combination of trametinib (MEK 1/2 inhibitor) and radiation (14). The leading hypothesis to best explain the radiosensitization mechanism observed is that this combination acts on two tumor suppressor pathways at the same time. Specifically, the combination works to stabilize the p53 protein and activates the AMP-activated protein kinase (AMPK) depending on *LKB1* to ultimately induce senescence on cells. It is important to note that combination therapy was not effective in *KRAS*-mutated tumors that lack *STK11* mutations, including those with co-mutated *TP53*.

Although no therapies targeting *KRAS* mutations in NSCLC have been formally approved by the FDA to date, recently published data of a phase 1 trial of sotorasib showed promising clinical benefit in patients with advanced solid tumors harboring the *KRAS* G12C mutation. In fact, 32% of the patients in the subgroup with NSCLC had a confirmed objective response to therapy, despite being heavily pre-treated (3). Future research should consider how best to integrate *KRAS*-targeting therapy into the treatment paradigm for earlier stages of disease.

### **EGFR- and ALK-mutant NSCLC**

Pre-dating the PACIFIC trial, Tanaka *et al.* demonstrated that *EGFR* mutation status offers predictive insight on the response to definitive CCRT in unresectable stage III NSCLC (15). This is an important concept to explore as retrospective studies suggest that up to 30% of patients in some populations with locally advanced NSCLC harbor an *EGFR* mutation (16,17). Tanaka *et al.* performed a retrospective analysis and found that PFS in patients treated with CCRT was significantly shorter in those with *EGFR*-mutated NSCLC as compared to their wild-type counterparts [median PFS (mPFS) 9.8 *vs.* 16.5 months,  $P=0.041$ ] (15). The investigators also noted that *EGFR*-mutated NSCLC was more likely to develop distant metastases after CCRT as compared to wild-type *EGFR* lung adenocarcinomas, with the brain being the most common site in *EGFR*-mutant patients (35%). Interestingly, locoregional recurrence was lower in *EGFR*-mutant patients than for their wild-type counterparts (14% *vs.* 35%,  $P=0.027$ ). The higher frequency of distant metastases, particularly in the brain, suggests an intrinsic brain tropism of the *EGFR*-mutant

tumors; one can hypothesize that CCRT with or without durvalumab consolidation is likely not penetrating the blood-brain barrier as effectively.

To better understand the impact of *EGFR* and *ALK* mutations on definitive CCRT, Nakamura *et al.* evaluated 173 patients with lung adenocarcinoma, 34 with *EGFR*-mutated disease and 13 with *EML4-ALK* translocation (18). The investigators again found that in the *EGFR*-mutant group, there was a significantly lower rate of in-field failure ( $P=0.027$ ), however, there was a higher rate of out-of-field failure ( $P=0.029$ ) as compared to the wild-type *EGFR* adenocarcinoma group. This suggests that *EGFR*-mutated adenocarcinoma may be more chemoradiosensitive. There was no significant difference in rates of in-field or out of field failure between the *ALK*-translocated and wild-type *ALK* groups, albeit the numbers were small. Interestingly, the 3-year OS rate was significantly higher for *EGFR*-mutant patients than their wild-type counterparts (75% *vs.* 46%;  $P=0.002$ ); this is likely because patients in the *EGFR*-mutant group received tyrosine kinase inhibitors (TKIs) after recurrence; while the wild-type group went on to receive salvage chemotherapy. Limitations of this study should be acknowledged, including its retrospective nature and small sample size. Nevertheless, this study hints that molecular profiling of the tumor may offer insight on the likelihood of recurrence after definitive CCRT in our locally advanced unresectable NSCLC patients. It also raises the question of whether similar strategies may be viable for patients harboring other targetable mutations (i.e., *MET*, *RET*, *ROS1*, *BRAFV600E*, etc.)

### **KEAP1- or NRF2-mutant squamous cell carcinomas (SCC)**

Focusing specifically on the treatment of SCC of the lung, a subtype of NSCLC, studies have been conducted to improve upon the resistance to radiation therapy that *KEAP1* or *NRF2* mutations induce, as previous investigation has shown increased radiotherapy resistance in tumors harboring this specific subset of mutations. The *KEAP1-NRF2* pathway plays a protective role against oxidative stress. Specifically, *NRF2* is a transcription factor that is normally bound by the adapter protein *KEAP1*. When oxidative stress is present, *NRF2* is released from *KEAP1* and subsequently translocates into the nucleus to induce transcription of genes that defend against reactive oxygen species (ROS). Mutations in *KEAP1* or *NRF2* are present in more than one third of patients with SCC of the lung. Previous studies have shown that the *KEAP1* or *NRF2* pathway and production of ROS affect the

**Table 2** Selected biomarker-driven trials for patients with locally advanced NSCLC

Trial	Phase	Estimated number of patients	Biomarker for eligibility	Radiation type	Systemic treatment
WJOG6911L	2	27	<i>EGFR</i>	Conventional	Gefitinib
LOGIK0902/OLCSG0905	2	46	<i>EGFR</i>	Conventional	Gefitinib induction followed by CCRT
NCT01391260	2	30	<i>EGFR</i>	Conventional	Gefitinib
RT0901	2	75	<i>EGFR</i>	Conventional	Erlotinib
NRG-LU004	1	24	PD-L1 >50%	Accelerated hypofractionated or conventional fractionated	Durvalumab
SPRINT	2	63	PD-L1	Conventional	Pembrolizumab (PD-L1 ≥50%) or conventional CCRT (PD-L1 <50%)

CCRT, concurrent chemotherapy and radiation therapy.

development and growth of lung cancer; additional studies have also demonstrated the effects of *KEAP1* or *NRF2* mutations on treatment resistance, with one hypothesis being that high levels of ROS can lead to suppression of CD8<sup>+</sup> T cells, resulting in suppression of the overall immune system and ultimately treatment resistance (19). Jeong *et al.* developed a murine model of SCC of the lung and demonstrated that deletion of *KEAP1* or *Trp53* (TP53 in humans) promotes resistance to radiation therapy in this specific subset of patients (20). Specifically, the investigators found that *KEAP1/NRF2* mutation status is predictive of the rate of local progression after radiotherapy in SCC of the lung. Their results are clinically meaningful and suggest that patients with *KEAP1* or *NRF2* alterations might benefit from radiation dose escalation, an alternate modality of local therapy, or inhibition of *NRF2* targets to allow for radiosensitization. Prospective studies are needed to further investigate a more personalized treatment approach for this subset of patients.

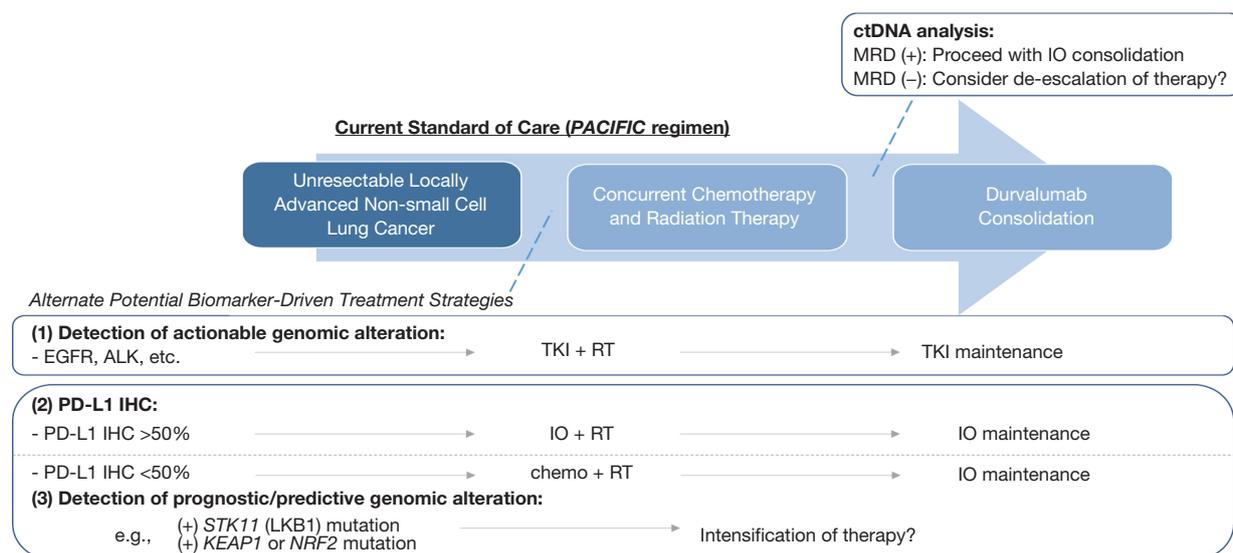
### Emerging treatment strategies

Additional studies using various biomarker-based strategies are already underway with the hope to redefine treatment of our patients with locally advanced NSCLC (Table 2). With the reported differences in response to CCRT based on *EGFR* and *ALK* mutation status, several trials are investigating the role of TKIs in the treatment of locally advanced NSCLC, both in the consolidation phase and in lieu of platinum-based chemotherapy. As an example, Akamatsu *et al.* are enrolling 27 patients in the single arm phase II study WJOG6911L, which will investigate the efficacy and safety of concurrent gefitinib and thoracic radiotherapy in locally advanced *EGFR*-mutant NSCLC (21). The rationale for the trial is sound as the use of *EGFR*-TKIs as compared to platinum-doublet chemotherapy has a significantly improved objective response rate (ORR)

in the treatment of metastatic NSCLC; preclinical study also suggests that gefitinib has a radio-sensitizing effect (22). The primary endpoint is PFS at 2 years with key secondary endpoints to include ORR, PFS, OS, and safety. Other noteworthy studies among several that will specifically focus on patients with *EGFR*-mutant locally advanced NSCLC include the phase II LOGIK0902/OLCSG0905 intergroup study evaluating the use of induction gefitinib monotherapy followed by CCRT, phase II NCT01391260 studying concurrent gefitinib and thoracic radiation therapy, and the phase II RT0901 trial evaluating concurrent erlotinib and thoracic radiation therapy.

Further attempts to move away from platinum-based chemotherapy using a biomarker directed approach include the NRG-LU004 phase I trial. Specifically, the NRG-LU004 trial will evaluate the safety of conventionally fractionated or accelerated hypofractionated radiotherapy in combination with durvalumab (in lieu of chemotherapy) in locally advanced NSCLC patients with a high PD-L1 expression of 50% or greater. Patients will be randomized to receive radiation therapy as 60 Gy in 30 fractions or 60 Gy in 15 fractions. Similarly, the phase II SPRINT trial (NCT03523702) will evaluate replacing concurrent chemotherapy with immunotherapy, albeit with pembrolizumab, in patients with a high (≥50%) PD-L1 expression (23).

Finally, it is also important to think about how we can use biomarkers in the post-treatment setting, not only to evaluate treatment response, but to also tailor subsequent treatment strategies. Moding *et al.* explored how the use of circulating tumor DNA (ctDNA) molecular residual disease (MRD) may improve outcomes for our patients with locally advanced NSCLC (24). The investigators performed deep sequencing ctDNA analysis on 218 samples obtained from 65 patients receiving CCRT for locally advanced NSCLC; 28 of these patients were receiving consolidation



**Figure 1** Potential biomarker-based treatment strategies for unresectable locally advanced NSCLC. The current standard of care for treatment of patients with unresectable locally advanced non-small cell lung cancer (NSCLC) per results of the PACIFIC trial is highlighted in the blue arrow above, and demonstrates definitive concurrent chemotherapy and radiation therapy (CCRT) followed by durvalumab consolidation, irrespective of PD-L1 expression. Alternatively, the figure above depicts potential biomarker-driven treatment strategies to consider in lieu of the current standard of care by evaluating for actionable genomic alterations, PD-L1 IHC expression, and/or other prognostic/predictive genomic alterations at time of diagnosis. Circulating tumor DNA (ctDNA) analysis for evidence of minimal residual disease (MRD) could also play an important role in treatment decision making after completion of definitive CCRT to either proceed with durvalumab consolidation or consider a de-escalation of therapy. IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor; RT, radiotherapy; IO, immunotherapy.

durvalumab. The authors found that patients with undetectable ctDNA after CCRT had favorable outcomes, irrespective of subsequent consolidation immunotherapy. On the other hand, patients with MRD after CCRT had better outcomes with consolidation immunotherapy as compared to those who did not. Their work suggests that ctDNA MRD may serve as a post-treatment biomarker to assess response to treatment and potentially help us decide which patients should receive consolidation immunotherapy as a preliminary attempt to de-escalate treatment

## Conclusions

The PACIFIC study was the first trial to demonstrate a survival benefit with the use of immunotherapy in earlier-stage NSCLC. As a result, consolidation immunotherapy after CCRT has become the standard of care for our patients with unresectable locally advanced NSCLC, regardless of PD-L1 expression. Multiple clinical trials are being developed or are already underway to evaluate the addition of upfront immunotherapy to CCRT (i.e., DETERRED, PACIFIC2, KEYNOTE-799, NICOLAS). Alternatively, there are several studies investigating the replacement of concurrent chemotherapy, either with

immunotherapy (based on level of PD-L1 expression) or targeted therapies (based on tumor mutational status) (25). We acknowledge that many of the studies cited in our discussion evaluated a small sample size. Thus, there are limitations with interpretation and the ability to arrive at definitive conclusions. Nevertheless, these studies are informative as responses to targeted therapy are typically homogenous. Therefore, these studies are useful and suggest potential methods for incorporating biomarkers into the future management of patients with locally advanced unresectable NSCLC. Larger studies are still needed to better understand the evolving role of utilizing biomarkers in this setting.

As we think ahead about the future management of NSCLC, research in this field has already begun to move away from utilizing nonselective cytotoxic chemotherapy to embracing a more personalized medicine type of approach. As such, the guidelines for treatment of patients with metastatic disease have largely shifted focus to the identification of targetable driver mutations and immune checkpoints. Future research is likely to explore novel ways to incorporate a more personalized approach to treatment in earlier stages of disease (Figure 1). Future research efforts should aim to (I) identify new targetable genetic mutations/

potential biomarkers and (II) utilize this information to optimize our treatment approach (i.e., combination therapy *vs.* maintenance therapy with a targeted agent etc.) to improve upon treatment outcomes, while reducing treatment-associated toxicities.

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